REMARKS

In accordance with the present invention, there are provided methods for treating hyperplasia in subjects in need thereof. In another aspect of the invention, there are provided methods for reducing neointimal hyperplasia associated with vascular interventional procedures. In addition, there are provided formulations useful in the above-described methods. Formulations contemplated for use herein comprise at least one pharmaceutically active agent coated with a protein.

By the present communication, claims 1, 9, 17, 18, 25 and 29-30 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims (see, for example, parent application, published as WO99/00113, at p. 42, lines 23-26; copy of page 42 provided herewith for the Examiner's convenience). Accordingly, claims 1-30 remain pending.

The rejection of claims 18 and 20-28 under 35 U.S.C. 102(e) as allegedly being anticipated by Shashoua et al., U.S. 5,795,909 (1998) is respectfully traversed. Applicants' invention, as defined by claim 18, distinguishes over Shashuoa by requiring a composition comprising a drug coated with a protein. Shashuoa does not disclose such a composition. In contrast, Shashuoa requires drug to be conjugated or chemically/covalently linked to a carrier molecule (i.e., cis-docosahexanoic acid (DHA)). See, for example, column 4, lines 9-12 of Shashuoa where it is stated that "a covalent conjugate of cis-docosahexanoic acid and a pharmaceutical agent effective for treating said condition is administered to a subject in need . . . ". Thus, it is clear that Shashuoa requires drug to be covalently linked to the carrier molecule, DHA.

The discussion at page 2, third paragraph of the Office Action reflects an apparent misunderstanding of the Shashuoa disclosure. Thus, the Examiner's assertion that Shashuoa teaches that "pharmaceutical agents may be conjugated to the drug compound (column 19, lines 62-67), such as anti-dorsalizing morphogenetic protein-1 (column 31, lines 47-48), single-chain antigen binding protein (column 33, line 12), and somatomedin

binding protein (column 33, line 14)" is r spectfully submitted to be in err r. C ntrary to the Examiner's assertion, Shashuoa describes a covalent c njugate of DHA (and not a pharmaceutical agent) with virtually any drug compound (column 19, line 62). In other words, Shashuoa teaches the use of DHA, "a lipophilic 22-carbon unbranched fatty acid" (column 3, lines 40-41) as a carrier molecule for drugs to "help deliver them across the blood-brain barrier" (column 3, lines 42-43) and to target these conjugates to "colon tissue, breast tissue, and central nervous system tissue" (column 3, lines 58-59).

Moreover, the Examiner's assertion (quoted above) that "pharmaceutical agents may be conjugated to the drug compound. . . " is a clear misrepresentation of Shashuoa's teaching. What Shashuoa actually teaches is that "DHA may be conjugated to virtually any drug compound" (column 19, line 62). Pharmaceutical agents contemplated by Shashuoa refers to any drug or drug compound such as those presented in the exhaustive list starting at column 4, line 21 or column 20, line 47. In other words, as used by Shashuoa, "pharmaceutical agents" and "drug compound" are one and the same.

The proteins noted above by the Examiner and by Shashuoa are in fact examples of the "drug compound" or "pharmaceutical agents" to be conjugated with the carrier, DHA. Thus, Shashuoa does not teach combining a drug with a protein as required by the present claims. Instead, Shashuoa only teaches combination of the non-protein carrier, DHA, with specific pharmacologically active proteins as discussed above. In view of the above remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. 102(e) are respectfully requested.

The rejection of claims 1-8, 17-24 and 29-30 under 35 U.S.C. 103(a) as allegedly being unpatentable over Shashuoa et al., is respectfully traversed. Applicants' invention, as defined by claim 1, distinguishes over Shashuoa by requiring treating hyperplasia with an effective amount of a defined drug composition, i.e., a composition comprising drug coated with a protein. Shashuoa does not disclose or suggest treating any indication with such a composition. Instead, Shashuoa only teaches the use of a conjugate of DHA with a protein, wherein the protein is the drug or pharmaceutical agent.

Applicants' invention, as defined by claim 17, further distinguishes over Shashuoa by requiring a method to reduce proliferation and cell migration in a subject undergoing a vascular interventional procedure. Such method comprises systemically administering a defined formulation to said subject, wherein the defined formulation comprises a drug that inhibits proliferation and cell migration, coated with a protein. Shashuoa does not disclose or suggest such a formulation nor any such uses therefor.

Applicants' invention, as defined by claim 18, still further distinguishes over Shashuoa by requiring a composition for treatment of hyperplasia, said composition comprising at least one drug coated with a protein. Shashuoa does not disclose or suggest such a composition nor any uses therefor.

Applicants' invention, as defined by claim 29, yet further distinguishes over Shashuoa by requiring a method to reduce the toxicity of a drug that inhibits proliferation and migration of cells, by combining said drug with a biocompatible protein such that the drug is coated with said protein. Shashuoa does not disclose or suggest such methods.

Applicants' invention, as defined by claim 30, further distinguishes over Shashuoa by requiring a pharmaceutical formulation with reduced toxicity. Such formulations comprise a drug that inhibits proliferation and cell migration, coated with a biocompatible protein. Shashuoa does not disclose or suggest such formulations.

In view of the above remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a) over Shashuoa are respectfully requested.

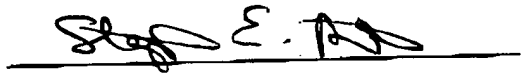
The rejection of claims 9-16 and 25-28 under 35 U.S.C. 103(a) as allegedly being unpatentable over Shashuoa et al., further in view of Li, et al., U.S. Patent No. 5,977,163 (1999) is respectfully traversed. Applicants' invention, as defined by Claim 9, distinguishes over the art by requiring a method for reducing neointimal hyperplasia associated with vascular interventional procedures in a subject in need thereof. Invention methods comprise administering to the subject an effective amount of a defined c mposition, i.e., a composition c mprising drug coated with a protein.

Applicants' inventi n, as defined by claim 25, further distinguishes over the art by requiring a c mposition for reducing neointimal hyperplasia ass ciated with vascular interventional procedures. Invention compositions comprise at least one drug coated with a protein.

As discussed above, Shashuoa does not disclose or suggest invention compositions, nor methods for use thereof. Further reliance on Li, et al. is unable to cure the deficiencies of Shashuoa. As with Shashuoa, Li does not disclose or suggest compositions comprising drug coated with a protein. Instead, Li employs conjugates of drug, i.e., paclitaxel or docetaxel covalently linked to carriers such as polyglutamic acids or polyaspartic acids.

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

By 

Stephen E. Reiter
Attorney for Applicant
Registration No. 31,192

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FOLEY & LARDNER
P.O. Box 80278
San Diego, California 92138-0278
Telephone: (858) 847-6711
Facsimile: (858) 792-6773

Enclosure

paclitaxel suitable for administration of paclitaxel to a subject in need thereof, said formulation comprising paclitaxel in a pharmaceutically acceptable formulation free of cremaphor.

In accordance with a still further embodiment of the present invention, there is provided a lyophilized formulation of paclitaxel suitable for administration of paclitaxel to a subject in need thereof upon reconstitution.

In accordance with a still further embodiment of the present invention, there is provided a frozen formulation of paclitaxel suitable for administration of paclitaxel to a subject in need thereof upon thawing.

In accordance with a still further embodiment of the present invention, there is provided a liquid formulation of paclitaxel comprising water and paclitaxel at a concentration of at least 2.0 mg/ml.

In accordance with a still further embodiment of the present invention, there is provided a drug delivery system comprising particles of a solid or liquid, substantially water insoluble pharmacologically active agent, coated with a protein,

wherein said protein coating has free protein associated therewith,